

## Short report

### Rituximab therapy in Waldenstrom's macroglobulinemia: Preliminary evidence of clinical activity\*

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#### Summary

To assess the preliminary efficacy of rituximab therapy in Waldenstrom's macroglobulinemia (WM), we examined the clinical and laboratory data for all patients with WM treated on IDEC Pharmaceuticals sponsored trials and one patient treated at Walter Reed Army Medical Center. Seven symptomatic patients with WM were treated with four ( $n = 6$ ) or eight ( $n = 1$ ) weekly infusions of rituximab ( $375 \text{ mg/m}^2$ ). Patients had received a median of three prior therapies (range 1–4) which included alkylator therapy in all (five patients refractory) and fludarabine in four (all refractory). Therapy was tolerated well in all patients without decrement in cellular

immune function or significant infectious morbidity. Partial responses were noted in three of these patients, including two with fludarabine-refractory disease. The median progression-free survival for these patients was 6.6 months (range 2.2–29+ months). These data suggest that rituximab has clinical activity in heavily pre-treated patients with Waldenstrom's macroglobulinemia. Based on these data, clinical studies of Rituximab in previously untreated and treated WM appear indicated.

**Key words:** anti-CD20, monoclonal antibodies, non-Hodgkin's lymphoma, Rituxan, Rituximab, Waldenstrom's macroglobulinemia

#### Introduction

Waldenstrom's macroglobulinemia (WM) is a clonal B-cell lymphoproliferative disorder characterized by production of IgM paraproteinemia, organomegaly, cytopenias, and symptoms of hyperviscosity [1, 2]. While commonly grouped with chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone lymphoma, and mantle-cell lymphoma in the broad small lymphocytic lymphoma category of the Working Formulation (IWF type A), WM has been identified as a unique entity in the Revised European-American Lymphoma (R.E.A.L.) Classification where it represented 1% of all lymphomas presenting for clinical evaluation [3]. Therapy for symptomatic patients with WM includes alkylator therapy which generally produces approximately a 50% response rate as initial therapy [4]. The purine analogs fludarabine and cladribine have significant activity in both untreated and alkylator-refractory WM [5–7]. Unfortunately, these agents produce cytopenias and cellular immune dysfunction [8]. Effective therapeutic options for patients failing these therapies are unavailable, making identification of new treatments of great importance.

Rituximab (IDEC-C2B8, Rituxan<sup>®</sup>), a chimeric antibody directed against CD20, is approved for use against relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL). Phase II studies of Rituximab demonstrated high response rates (48%–62%) in relapsed low-grade NHL [9–11]. Herein, we report rituximab treatment in WM demonstrating preliminary efficacy of this therapy without the usual toxicity seen with other therapies employed in this disease.

#### Patients and methods

The clinical features of adult patients with relapsed low-grade NHL enrolled on four serial trials performed by IDEC Pharmaceuticals were examined. From these trials, six patients with working formulation A histology and elevated IgM paraproteinemia ( $> 500 \text{ mg/dl}$ ) were identified. The eligibility criteria for these patients has been described which included positive CD20 expression on tumor cells [10, 11]. An additional single patient with WM treated at Walter Reed Army Medical Center is included. For purposes of this analysis, patients were considered refractory to a therapy if they failed to respond or relapsed within six months of completing therapy with the respective agent.

All patients received rituximab at a dose of  $375 \text{ mg/m}^2$ , administered intravenously once weekly for four ( $n = 6$  patients) or eight ( $n = 1$

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patient) weeks. Administration of the antibody followed guidelines set forth previously [10]. The specific baseline evaluation and serial monitoring of patients enrolled on the IDEC studies has been previously described [10, 11].

Criteria for response included: complete response required resolution of all symptoms, measurable disease and disappearance of IgM monoclonal protein for a period of one month. Partial response (PR) required a > 50% reduction in the sum of the products of perpendicular measurements of the lesions, without evidence of progressive disease for at least one month and a 50% or greater reduction in the IgM paraproteinemia. Patients demonstrating either development of new sites of disease or 25% or greater increase in measurable disease (including paraproteinemia) were considered to have progressive disease. Response duration was measured from the time response was noted until the date progressive disease was noted. Time to progression was measured from the date of the first rituximab infusion until the date progressive disease was noted. Comparison of pre- and post-therapy lymphocyte subsets were performed utilizing the students paired *t*-test.

## Results

The pre-treatment characteristics of the seven WM patients are summarized in Table 1. These patients were elderly with a median age of 60 years (range 50–75) with 5 being female. All were symptomatic with a median performance status of 1 (range 1–3). Measurable disease and bone marrow infiltration was present in all patients, irrespective of the WM associated paraproteinemia. All of these patients were heavily pre-treated, having received a median of 3 (range 1–4) prior therapies. Most notably, five were alkylator refractory and four were refractory to prior treatment with fludarabine. Five were refractory to the last therapy administered.

All seven patients with WM received their designated four ( $n = 6$ ) or eight ( $n = 1$ ) weekly treatments with Rituximab. Partial responses were noted in three (43%) of patients with a fourth patient having greater than a 50% decline in measurable disease, but less than a 50% reduction in the IgM paraproteinemia. Pre-treatment characteristics of these three patients included two with fludarabine-refractory disease and all being refractory to their last therapy. The response duration for these patients was 2, 11, and 29+ months. Improvement was noted in all responding patients at the one-month follow-up visit post-Rituximab, although improvement was often noted prior to this. Specifically, normalization of platelet count was noted in the two patients with thrombocytopenia. Bone marrow involvement resolved in only one patient. The mean progression-free survival for all seven patients was 6.6 months (range 2.2–29+ months).

Rituximab therapy was well tolerated, with five patients experiencing some infusion related toxicity. This was mild in four (grade 1) and moderate in one (grade 3) patient who had fevers chills and transient bronchospasm. These symptoms resolved with temporary cessation of the infusion. Other toxicity was mild including grade 1 diarrhea (1 patient) and grade 1 abdominal pain (1 patient). Hematologic toxicity was absent. Cellular immune function as measured by changes in CD4 or

Table 1 Patient characteristics.

Age (in years)	
Median	60
Range	50–75
Sex	
Male	2
Female	5
Performance status	
Median	1
Range	1–3
Number of prior therapies	
Median	3
Range	1–4
Number of treated with alkylator agent	7
Number of refractory to alkylator therapy	5
Number of treated with fludarabine	4
Number of refractory to fludarabine	4
Number of refractory to last treatment	5
IgM (g/dl)	
Mean	2.9
Range	0.72–6.28
Bone marrow involvement	7
Leukocyte count (/cm <sup>3</sup> )	
Mean	5.1
Range	3.0–6.6
Hemoglobin count (g/dl)	
Mean	10.5
Range	8.6–13.4
Platelet count (/cm <sup>3</sup> )	
Mean	219
Range	32–332

CD8 T-cell populations was not altered by rituximab. Specifically, the mean CD4 lymphocyte count pre-treatment was 344/mm<sup>3</sup> as compared to 331/mm<sup>3</sup> three months post-treatment ( $P = 0.89$ ). Similarly the mean CD8 count was 608/mm<sup>3</sup> pre-treatment as compared to 654/mm<sup>3</sup> post-treatment ( $P = 0.32$ ). Only one infection was noted in these seven patients from the time of treatment until progression, a grade 3 bacterial sinusitis. One patient developed localized varicella zoster eleven months after treatment with Rituximab at the time disease progression was noted.

## Discussion

Herein we have described preliminary data suggesting Rituximab may have activity in patients with previously-treated and purine-analog refractory WM. Treatment options for patients with WM are limited, with no curative options being available. Alkylator therapy has been extensively used with a partial response rate of 50% or less in most series [3]. The purine analogs fludarabine and cladribine produce objective responses in greater than 50% of patients with previously untreated disease and approximately 30%–40% alkylator refractory WM, but only rarely produce complete responses. Furthermore, both the purine analogs and alkylator therapy produce cytopenias and cellular immune dysfunction that can lead to a predisposition to developing both bacterial and opportunistic infections [7, 8]. Therapy

after failure of cladribine or fludarabine in Waldenstrom's macroglobulinemia is limited, with no currently accepted option.

Rituximab is a selective chimeric monoclonal antibody directed against the cell surface antigen CD20. It has demonstrated efficacy in patients with low-grade or follicular lymphoma, where responses have been noted in approximately 50% of individuals treated. By virtue of Rituximab's selectivity for B lymphocytes, studies to date in lymphoma have shown it lacks adverse events such as myelosuppression, and alteration of T-cell subsets that are observed with other therapies utilized in Waldenstrom's macroglobulinemia [7]. Indeed, our data demonstrates this is also true in patients with WM, where we noted no significant myelosuppression or depletion of T-cell subsets in the patients examined. Toxicity with this therapy was mild and not life threatening, with three of seven (43%) patients responding to treatment. Two of these responses occurred in patients with fludarabine-refractory disease, for which no effective therapy exists.

Patients in this series were selected for Working Formulation A classification, identified retrospectively, and all had measurable lymphadenopathy. Generalization of these preliminary data to the WM patient population who may have different immunophenotype, clinical features, and working formulation classification should not occur. In particular, these patients may have circulating tumor cells in the blood (none of the described patients had this) which may increase the risk for infusion-related events [12]. These data do provide support for clinical trials of Rituximab in both untreated and purine analog-refractory Waldenstrom's macroglobulinemia. Definitive conclusions regarding the efficacy of Rituximab in WM should be deferred until such studies are completed. Nonetheless, these data suggest that Rituximab may have significant efficacy in the treatment of WM.

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